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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,095	03/18/2004	Nasrin Mesaeli	81190-2602	1202

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,095	MESAELI, NASRIN	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,14,17-19* is/are pending in the application.

4a) Of the above claim(s) *6-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,14 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 16, 2006 has been entered.

Claims 2, 5, 12, 13, 15, 16 are cancelled. Claims 6-11 are withdrawn. Claims 1, 3, 4, 14, 17-19 are amended.

Claims 1, 3, 4, 14, 17-19 are under consideration.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 14, 17 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a transgenic mouse whose genome comprises a transgene comprising mouse SM22-alpha promoter operably linked to a cDNA encoding a mouse calreticulin (CRT) peptide having an amino acid sequence with 93% homology to SEQ ID NO:23, wherein

expression of calreticulin from the mouse SM22-alpha promoter in the vascular smooth muscle cells of the transgenic mouse results in hemangioma formation,

2) a transgene comprising mouse SM22-alpha promoter operably linked to a cDNA encoding mammalian calreticulin (CRT) peptide,

3) a method for producing a transgenic mouse that exhibits hemangioma comprising:

introducing into a fertilized mouse egg a transgene comprising mouse SM22-alpha promoter operably linked to a cDNA encoding a mammalian calreticulin (CRT) peptide,

does not reasonably provide enablement for

1) a transgenic mouse whose genome comprises a transgene comprising mouse SM22-alpha promoter operably linked to a cDNA encoding a mouse calreticulin peptide, said peptide having at least 80% homology to SEQ ID NO. 23,

2) a method for producing a transgenic mouse that exhibits hemangioma comprising:

introducing into a fertilized mouse egg a transgene comprising mouse SM22-alpha promoter operably linked to a cDNA encoding a mouse calreticulin (CRT) peptide, said peptide having at least 80% homology to SEQ ID NO. 23.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, November 16, 2005 and May 6, 2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Response to Arguments

Applicant's arguments, see page 1 of Remarks, filed February 16, 2006, with respect to the rejection of claims 1, 3, 4, 14, 17 under 35 U.S.C. 112, first parag. have been fully considered and are persuasive in part.

Applicant provides an argument that the art provides support for an artisan to practice the claimed invention for its full breadth of "at least 80% homology to SEQ ID

NO. 23 (Applicant's response, page 1)" as an artisan could, on comparison of the mouse CRT sequence could obtain the CRT sequence from dog and monkey and determine which amino acid residues are highly conserved and which are more likely to tolerate conserved changes. . The specification provides guidance for an artisan to express rabbit CRT in the vascular smooth muscle cells (VSMC) of the transgenic mouse model that exhibits hemangioma. A sequence search of SEQ ID NO. 23 (rabbit CRT) has indicated human, rat, mouse CRT amino acid sequences to be 93% or more identical to that of SEQ ID NO. 23. . However, the broader scope of 80% homology to SEQ ID NO. 23 is not enabled for the following reason. The scope of 80% homology encompasses any amino acid differences, anywhere in SEQ ID NO. 23, wherein the sequences differ up to 20%. This means that in addition to encompassing amino acid sequences that are similar to dog or monkey CRT, "80% homology" also encompasses amino acid sequences which are not related to dog or monkey CRT and encode non-functional proteins or proteins that acquire activity unrelated to CRT. According to Michalak et al., 1999, Biochem J. 344: 281-292 (provided by Applicant in Applicant's response, August 29, 2005), "calreticulin has been implicated to participate in many (perhaps too many) cellular functions.... It is not surprising, therefore, that any changes in calreticulin expression and function have profound effects on many cellular functions (Michalak et al., page 284, 2nd col., under "Functions of Calreticulin")." As this applies to the instant invention, changes to calreticulin that lead to changes in calreticulin function would then lead to changes in phenotype of the claimed transgenic mice. Nothing in the art or the specification provides specific guidance in obtaining a mouse CRT amino acid

sequences that predictably result in hemangioma in the mouse model, beyond wild type mouse CRT or a mouse CRT with at least 93% homology to SEQ ID NO:23.

Thus, for the reasons above, the specification does not provide guidance for an artisan to arrive at the claimed invention.

Claims 1, 3, 4, 14, 17 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicant's arguments, see page 1 of Remarks, filed February 16, 2006, with respect to the rejection of claims 1, 3, 4, 14, 17 under 35 U.S.C. 112, first parag. have been fully considered and are persuasive in part.

Similar to the enablement rejection above, the Examiner finds the Applicant's argument persuasive that there is written description for mammalian CRT; however, there is no sufficient written description for the full breadth of 80% homology to SEQ ID NO. 23. While the art provides guidance for obtaining CRT amino acid sequences for human, mouse, rat, and rabbit, neither the art nor the specification provide guidance for an artisan to arrive at amino acid sequences that have 80% identity to SEQ ID NO. 23, wherein when said amino acid sequences having any 80% identity to SEQ ID NO. 23

are expressed in VSMC of transgenic mice, would result in transgenic mice exhibiting hemangioma. As indicated by Michalak et al., CRT has many different biological functions. Should the function of CRT change, for example, via amino acid changes, this would result in profound biological effects. As such, while there is support in the art for mammalian CRT, there is no support for the full breadth of 80% homology to SEQ ID NO. 23. As the claims have been amended to recite "mouse CRT", the written description has been evaluated, based on the mouse sequence. A sequence search and analysis of SEQ ID NO. 23 indicates that there is 93.6% homology between the human sequence and SEQ ID NO. 23 (see copy of the search report). The bovine sequence has 90.3% homology but the bovine sequence has 18 fewer amino acids at the N-terminus than the rabbit sequence, and C-terminus has difference unlike that of the human, rat, and mouse sequence. As such, while the art provides written description for mouse calreticulin (CRT) peptide having an amino acid sequence with 93% homology to SEQ ID NO:23, the art does not provide guidance for sequences beyond 93% homology.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 14, 17-19 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A sequence search of SEQ ID NO. 23 has indicated that the sequence encodes rabbit CRT. The claims as written, are

drawn to mouse CRT. This is confusing because the phrase, "said peptide having at least 80% homology to SEQ ID NO. 23" is used to describe the mouse sequence as SEQ ID NO. 23.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER